



## Severe refractory asthma: current treatment options and ongoing research

**Menzella, Francesco; Bertolini, Francesca; Biava, Mirella; Galeone, Carla; Scelfo, Chiara; Caminati, Marco**

*Published in:*  
Drugs in Context (Online)

*Link to article, DOI:*  
[10.7573/dic.212561](https://doi.org/10.7573/dic.212561)

*Publication date:*  
2018

*Document Version*  
Publisher's PDF, also known as Version of record

[Link back to DTU Orbit](#)

*Citation (APA):*  
Menzella, F., Bertolini, F., Biava, M., Galeone, C., Scelfo, C., & Caminati, M. (2018). Severe refractory asthma: current treatment options and ongoing research. *Drugs in Context (Online)*, 7, [212561].  
<https://doi.org/10.7573/dic.212561>

---

### General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

## REVIEW

### Severe refractory asthma: current treatment options and ongoing research

Francesco Menzella MD<sup>1</sup>, Francesca Bertolini MSc, PhD<sup>2</sup>, Mirella Biava MSc<sup>3</sup>,  
Carla Galeone MSc<sup>1</sup>, Chiara Scelfo MD<sup>1</sup>, Marco Caminati MD<sup>4</sup>

<sup>1</sup>Department of Medical Specialties, Pneumology Unit, Arcispedale Santa Maria Nuova, Azienda USL di Reggio Emilia, IRCCS, Viale Amendola 2, 42122 Reggio Emilia, Italy; <sup>2</sup>Department of Bio and Health Informatics, Technical University of Denmark, DK-2800, Kgs. Lyngby, Denmark; <sup>3</sup>National Institute for Infectious Diseases 'L. Spallanzani', IRCCS, Via Portuense 292, 00149 Rome, Italy; <sup>4</sup>Asthma Center and Allergy Unit, Verona University Hospital, Piazzale L.A. Scuro, 37134 Verona, Italy

#### Abstract

Patients with severe asthma have a greater risk of asthma-related symptoms, morbidities, and exacerbations. Moreover, healthcare costs of patients with severe refractory asthma are at least 80% higher than those with stable asthma, mainly because of a higher use of healthcare resources and chronic side effects of oral corticosteroids (OCS). The advent of new promising biologicals provides a unique therapeutic option that could achieve asthma control without OCS. However, the increasing number of available molecules poses a new challenge: the identification and selection of the most appropriate treatment. Thanks to a better understanding of the basic mechanisms of the disease and the use of predictive biomarkers, especially regarding the Th2-high endotype, it is now easier than before to tailor therapy and guide clinicians toward the most suitable therapeutic choice, thus reducing the number of uncontrolled patients and therapeutic failures. In this

review, we will discuss the different biological options available for the treatment of severe refractory asthma, their mechanism of action, and the overlapping aspects of their usage in clinical practice. The availability of new molecules, specific for different molecular targets, is a key topic, especially when considering that the same targets are sometimes part of the same phenotype. The aim of this review is to help clarify these doubts, which may facilitate the clinical decision-making process and the achievement of the best possible outcomes.

**Keywords:** cytokines, economic burden, endotypes, eosinophils, inflammation, phenotypes.

#### Citation

Menzella F, Bertolini F, Biava M, Galeone C, Scelfo C, Caminati M. Severe refractory asthma: current treatment options and ongoing research. *Drugs in Context* 2018; 7: 212561. DOI: [10.7573/dic.212561](https://doi.org/10.7573/dic.212561)

## Introduction

Patients with severe asthma have an increased risk of asthma-related symptoms, morbidities, and exacerbations.<sup>1,2</sup> Moreover, healthcare costs of patients with severe refractory asthma are at least 80% higher than those with stable asthma because of a higher use of resources.<sup>3,4</sup> Approximately, up to 30% of patients with refractory asthma still require regular use of oral corticosteroids (OCS).<sup>5</sup> Prolonged use of OCS may lead to several side effects such as osteoporosis, fracture, infections, obesity, symptomatic coronary artery disease, avascular necrosis, stroke, cataract, glucose metabolism changes, and skin thinning.<sup>6</sup> In addition, there is an obvious concern about the adverse effects, especially growth, induced by OCS in children.<sup>7</sup> The potential side effects of OCS heavily affect patients' quality of life and sustain a big economical burden.

The advent of new promising biological therapies provides a strategy to avoid OCS damage and to improve global asthma control. For several years, the only available biologic therapy has been omalizumab, a monoclonal antibody (mAb) that targets immunoglobulin E (IgE) and is used for a specific subpopulation of patients with uncontrolled IgE-mediated allergic asthma. Recently, new drugs and nonpharmacologic options, such as anti-interleukin (IL)-5 mAbs, anti-IL-4/IL-13, and bronchial thermoplasty, are available as upcoming options, supported by encouraging results for patients not eligible or not responsive to omalizumab (Table 1). Due to the number of available treatment alternatives, the identification of the right drug for the right patient represents a key aspect of treatment, which can be implemented by new biomarkers reflecting an underlying disease mechanism, in addition to the correct use of those already available.

**Table 1. Biodrug options for severe asthma.**

Drug (Administration)		Regimen	Target population	Clinical outcomes
Anti-IgE	Omalizumab (Subcutaneous)	From 75 mg up to 1200 mg every 2/4 weeks	Early onset asthma. Serum total IgE levels $30 \leq \text{IgE} \leq 1500$ IU/mL Positive skin prick test or specific serum IgE for perennial allergens	Confirmed long-term efficacy both in adults and in children, antiviral effect, prevention of seasonal exacerbations
	Mepolizumab (Subcutaneous)	100 mg every 4 weeks	Eosinophilic asthma $\geq 300$ cells/ $\mu\text{L}$ , NP – CSWNP <sup>§</sup> , late onset asthma	Excellent safety profile, demonstrated clinical effect, and steroid-sparing effect
	Benralizumab (Subcutaneous)	30 mg every 4 weeks for the first 3 doses, then every 8 weeks	Eosinophilic asthma $\geq 300$ cells/ $\mu\text{L}$ , NP – CSWNP <sup>§</sup> , late onset asthma	High affinity for IL-5 receptor and ADCC activity, eosinophils total tissue depletion, improvement of pulmonary function
	Reslizumab (Intravenous)	3 mg $\text{kg}^{-1}$ every 4 weeks	Eosinophilic asthma $\geq 300$ cells/ $\mu\text{L}$ , NP – CSWNP <sup>§</sup>	Personalized dosage and improvement of pulmonary function
Anti-IL-4/ IL-13	Dupilumab (Subcutaneous)	300 mg every 4 weeks	Eosinophilic asthma $\geq 150$ –300 cells/ $\mu\text{L}$ , aspirin-exacerbated respiratory disease (AERD)*	Significant steroid-sparing effect and improvement of pulmonary function

\*Aspirin-exacerbated respiratory disease (AERD): defined by a physician diagnosis of asthma, chronic rhinosinusitis with nasal polyposis, and a convincing clinical history of nonsteroidal anti-inflammatory drug (NSAID) sensitivity.

<sup>§</sup>CSwNP, chronic sinusitis with nasal polyposis; NP, nasal polyposis.

ADCC, antibody-mediated cell cytotoxicity; IgE, immunoglobulin E; IL, interleukin.

In this review, the management of available therapies and the overlapping aspects of some of those treatments as well as their application in clinical practice will be discussed. The future availability of new molecules that are specific for different targets is a key topic, especially when considering that the same targets are sometimes part of the same phenotype. It is important to address and clarify some of these aspects, which may further facilitate the clinical decision-making process to identify the most successful treatment option and obtain the best possible outcomes.

## Methods

For this review, a search strategy based on validated keyword filters was devised to select articles regarding severe asthma and its management. In detail, a selective search on medical databases (in particular PubMed and Medline) was carried out up to February 2018, and research papers, international guidelines, recommendations, position papers, systematic reviews, and Cochrane meta-analyses relevant to the topic have been considered. The search strategy was based on the following keywords: inflammation, asthma phenotypes, asthma endotypes, T2-low and T2-high subtypes, IgE, eosinophils, cytokines, IL-5, IL-4, IL-13, and costs. A total of 245 potential papers were identified in the first search through databases, and 115 of these were considered eligible. Only original studies with human subjects were considered, and

only full texts were included among those potentially relevant. Case reports and purely descriptive studies were excluded.

## Severe asthma treatments: Th2 versus non-Th2

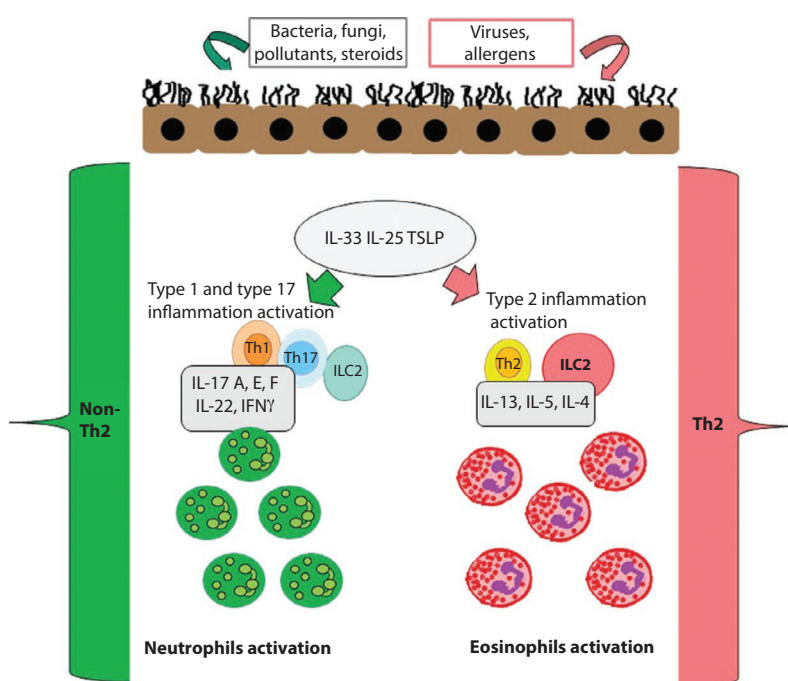
Asthma is recognized as a complex condition with differences in severity, natural history, comorbidities, and treatment response. A longstanding debate in the asthma field is whether asthma is a single disease with a variable presentation, or several diseases that have variable airflow obstruction as a common feature.<sup>8</sup> Therefore, different definitions have been proposed based on the ‘observable characteristics’ – the phenotypes – which describe clinical, physiological, morphologic, and biochemical characteristics as well as the response to different treatments.<sup>9</sup> However, even if clinically relevant, phenotypes do not provide any insight on the underlying disease mechanism. Thus, in relation to asthma heterogeneity, the term ‘endotype’ has recently been introduced to describe ‘a subtype of a condition defined by a unique or distinctive functional or pathophysiologic mechanism’.<sup>10</sup>

Currently available treatments and most of the upcoming ones are directed to the inflammatory Th2 endotype that drives the inflammation in about 50% of asthma patients.<sup>6</sup> The mechanisms underlying the dysregulation of innate and adaptive Th2 immunity in severe asthma have been intensively analyzed in a recent review.<sup>11</sup> Cytokines, chemokines, and mediators involved in the Th2-signaling and inflammatory

**Table 2. Non-Th2 and Th2 strategies under investigation.**

Endotype	Target	Therapy	
Th2	IgE	Omalizumab	Available
	IL-5	Mepolizumab	
Th2	IL-5	Reslizumab	Under investigation
	IL-5R $\alpha$	Benralizumab	
	IL-13R $\beta$	Lebrikizumab	
	IL-4 $\alpha$	Dupilumab	
	IL-13	Tralokinumab	
	GATA3	GATA3 DNAzyme	
Non-Th2	Airways smooth muscle	Bronchial thermoplasty	Available
	TSLP	Tezepelumab	Under investigation
	PDG2 antagonist	Fevipirant	
	ILC2	Anti-CRTH2	
	Neutrophils	Anti-CXCR2	

CRTH2, chemoattractant receptor-homologous molecules expressed on Th2 cells; CXCR2, CXC chemokine receptor 2; IgE, immunoglobulin E; IL, interleukin; ILC2, type II innate lymphoid cells; PDG2, prostaglandin D2; Th, T helper 2; TSLP, thymic stromal lymphopoietin.

**Figure 1. Inflammatory pathway in asthma.**

IFN $\gamma$ , interferon gamma; IL, interleukin; ILC2, type II innate lymphoid cells; TH, T helper; TSLP, thymic stromal lymphopoietin.

pathways are almost all targeted by the available mAbs and other mediators will be targeted in the next future (Table 2).<sup>12</sup>

Regarding the neutrophilic non-Th2 endotype, currently there are not effective therapeutic options, even if some chemo-attractant antagonists for neutrophils have shown

promising results in early human trials.<sup>13</sup> Moreover, recent data are increasingly confirming the role of Th17 cells and IL-17: neutralization of IL-4 and/or IL-13 resulted in increased Th17 cells and neutrophilic inflammation in the lung, which confirms that Th2 and Th17 inflammatory pathways are reciprocally

regulated in asthma (Figure 1).<sup>14</sup> Other studies have highlighted the role of Group 2 innate lymphoid cells (ILC2s) in asthma pathogenesis and regulation of inflammation.<sup>15</sup> This enormous progress in understanding the inflammatory pathways could pave the way to the development of non-Th2 endotype target drugs in the next future (Table 2).

## Anti-IgE approach

In IgE-mediated asthma, allergens exposure, IgE antibodies, and their binding to high-affinity (FcεRI) and low-affinity (FcεRII or CD23) receptors on the surface of effector cells (mast cells and basophils) induce degranulation and release of cytokines and inflammatory mediators, which leads to the bronchoconstriction associated with asthma exacerbations.<sup>16</sup>

Omalizumab is a murine mAb that has been used in clinical practice since 2003 for the treatment of severe allergic refractory asthma in patients with serum IgE levels ranging between 30 and 1500 IU/mL. This mAb is the result of a somatic cell hybridization method and is able to bind to FcεRI and FcεRII receptors of basophils, dendritic cells, and mast cells.<sup>17</sup>

In the past decade, studies have confirmed the efficacy and safety of omalizumab, in terms of significant reduction in the frequency of asthma exacerbations (up to 50%), quality of life (QoL) improvement, and a significant steroid-sparing effect.<sup>18</sup> This mAb showed a good efficacy profile even in non-allergic asthma,<sup>19</sup> which can be explained by the possible existence of a local IgE production without systemic sensitization.<sup>20</sup> Recent studies have confirmed its effectiveness in pediatric patients with refractory asthma,<sup>21</sup> mainly in the prevention of seasonal exacerbations, thanks to the ability of omalizumab to restore interferon-α response to rhinoviruses.<sup>22</sup>

According to the available evidence, omalizumab treatment should be continued without suspension, as the IgE levels and the number of FcεRI receptors increase 3–4 weeks after its suspension, resulting in a worsening of asthma control, especially in patients with higher levels of eosinophilia, periostin, and fractional exhaled nitric oxide (FeNO).<sup>23</sup> In fact, the presence of these biomarkers seems to be related to a better response to omalizumab, but also to a more rapid loss of its effect after suspension, as shown in XPORT and EXTRA studies.<sup>23,24</sup> The prevention of exacerbations by omalizumab was greater in the presence of higher eosinophil levels, which represents an overlapping aspect between anti-IgE and anti-IL-5 mAbs. In a recent pooled analysis from two pivotal phase 3 trials, the authors found a better omalizumab response in patients with peripheral blood eosinophils levels  $\geq 300$  cells/ $\mu$ L.<sup>25</sup> In this subgroup, the treatment with omalizumab reduced exacerbations by 67% versus a 45% reduction of exacerbations in patients with values  $< 300$  cells/ $\mu$ L. However, greater disease severity, history of emergency asthma treatment, hospitalization, forced expiratory volume in 1 second (FEV<sub>1</sub>), % predicted, inhaled corticosteroids (ICS) dose, and long-acting beta-agonists (LABA) use, were associated with a

greater reduction in exacerbation by omalizumab. These data suggested that the preventive benefit may have been more related to disease severity, rather than to blood eosinophilia. A very recent retrospective real-life study conducted in France on 872 adult and pediatric patients with severe allergic asthma (STELLAIR) has come to different conclusions.<sup>26</sup> In this study, the response rate was calculated according to blood eosinophil count measured in the year prior to omalizumab treatment start. According to clinical evaluation, 67.2% of adults and 77.2% of minors were responders, while 71.1% of adults and 78.5% of minors had a  $\geq 40\%$  reduction in the exacerbation rate. In adults, the response rate for combined criteria was 58.4% for blood eosinophils  $\geq 300$  cells/ $\mu$ L and 58.1% for blood eosinophils  $< 300$  cells/ $\mu$ L. These data suggested that omalizumab response is unrelated to the level of blood eosinophilia, and therefore this biomarker should not be taken into consideration when choosing omalizumab as a treatment option.

Therefore, the correct selection of the patient for omalizumab implies not only a favorable response in the short term, but also an increase of clinical efficacy in the long term (up to 9 years of follow-up),<sup>27</sup> with a possible favorable cost-effectiveness profile in patients with refractory asthma, if correctly selected.<sup>28</sup>

## Anti-IL-5, anti-eosinophils, and the possible overlap with anti-IgE

Mepolizumab was the first biologic available for severe eosinophilic asthma. It is a humanized non-glycosylated IgG1 antibody blocking IL-5 and preventing the binding of IL-5 to its receptor. The first studies investigated the application of mepolizumab in diseases other than asthma, such as idiopathic hypereosinophilic syndrome and eosinophilic granulomatosis with polyangiitis (EGPA),<sup>29</sup> and demonstrated a significant reduction in the use of OCS and a better control of the disease. The dose of mepolizumab in EGPA is 300 mg instead of 100 mg for asthma. Early studies on asthma failed to reach the expected outcomes, as mepolizumab was ineffective in terms of improvement of respiratory function parameters (bronchial hyperresponsiveness, FEV<sub>1</sub>, peak expiratory flow – PEF) and reduction of exacerbation.<sup>30,31</sup> However, several studies underlined the presence of a bias in patients' recruitment, as they had not been properly stratified and selected according to their blood eosinophils and asthma severity. Subsequently, the DREAM, MENSA, and SIRIUS registrative randomized clinical trials (RCTs) showed the ability of this drug to significantly improve the control of asthma with a significant steroid-sparing effect in patients with severe asthma with blood eosinophils  $> 300$  cells/ $\mu$ L.<sup>32–34</sup> The MUSCA trial has confirmed that mepolizumab significantly improved the health-related QoL with an early improvement of pre-bronchodilator FEV<sub>1</sub> values sustained up to week 24.<sup>35</sup>

A *post hoc* analysis of DREAM and MENSA RCTs showed that baseline blood eosinophil count represents a biomarker predictive of mepolizumab clinical efficacy.<sup>36</sup> The authors



highlighted clinically relevant reductions in exacerbation rate in patients with a count of 150 cells/ $\mu$ L or more at baseline. Notably, this biomarker, although not specific, could lead to better patients' selection, especially for those who are likely to achieve important clinical improvement with mepolizumab. In addition, the drug demonstrated an excellent safety profile and a long-lasting and stable effect, as highlighted by the COSMOS study.<sup>37</sup>

Another anti-IL-5 is reslizumab, a humanized IgG4k mAb with high affinity for IL-5. This mAb addresses patients with uncontrolled eosinophilic asthma and blood eosinophil level >400 cells/ $\mu$ L, showing a meaningful reduction of sputum eosinophil count, improvement in QoL, FEV<sub>1</sub>, and reduction of exacerbation rate.<sup>38,39</sup>

A *post hoc* analysis of two identical pivotal trials (Studies 3082 and 3083) showed that patients with asthma, chronic sinusitis with nasal polyposis (CSwNP), and higher blood eosinophilia level (400 cells/ $\mu$ L) treated with reslizumab had 83% reduction of the annual rate of exacerbations compared to an overall reduction of 54%.<sup>40</sup> These data confirm a major clinical benefit of anti-IL-5 treatment in patients with higher eosinophilia levels and CSwNP. In an open-label extension trial, 1051 patients received intravenous (IV) 3.0 mg/kg reslizumab up to 2 years, with a good safety profile and sustained long-term efficacy in terms of lung function improvements and asthma control.<sup>41</sup> These results reinforce the evidence of long-term safety and efficacy in anti-IL-5 mAbs.

A practical limitation of this drug may be the IV administration route, as it implies the availability of a venous access, and the infusion over 20–50 minutes. Currently, the above-mentioned administration route and dosage are the only ones approved by Food and Drug Administration (FDA) and European Medicines Agency (EMA). However, recent data showed that a weight-adjusted dosage represents a potential added value, especially in overweight or obese patients. One study compared the response to weight-adjusted IV reslizumab in 10 prednisone-dependent patients with asthma who were previously treated with 100 mg mepolizumab subcutaneous (SC).<sup>42</sup> Reslizumab was shown to further reduce airway eosinophilia compared to mepolizumab SC, with a concomitant improvement in asthma control. Two ongoing phase 3 RCTs are evaluating the efficacy of reslizumab SC (ClinicalTrials.gov identifier: NCT02452190 and NCT02501629) and a phase 2–3 study is investigating the monthly infusion of 3 mg/kg IV reslizumab for 4 months in patients with prednisone-dependent eosinophilic asthma previously treated with another IL-5 antagonist (mepolizumab) administered subcutaneously (ClinicalTrials.gov identifier: NCT02559791).

Benralizumab is a IgA1 mAb that binds the epitope on the  $\alpha$ -subunit of the IL-5 receptor. It reduces blood eosinophils and their precursors through a completely different mechanism compared to other IL-5 antagonists, based on the induction of antibody-mediated cell cytotoxicity (ADCC).<sup>43,44</sup> The constant region (Fc) of benralizumab is afucosylated, leading to a higher

affinity for the Fc-gamma III (Fc $\gamma$ RIIIa) receptor on the surface of mast cells, basophils, and natural killer cells. Through the last, it induces ADCC on eosinophils and basophils.<sup>45</sup> The result is an almost complete depletion of eosinophils in sputum and tissues (90% and 96%, respectively), as well as a total depletion in the bone marrow and in the blood.<sup>46</sup> In phase 1 and 2 randomized controlled trials, including patients with severe and peripheral eosinophilic asthma (eosinophils > 300 cells/ $\mu$ L), SC benralizumab showed excellent results, especially in terms of reducing inflammatory mediators, as well as causing a significant reduction of blood eosinophils.<sup>47–49</sup> Furthermore, different from other anti-IL-5 treatments, benralizumab is independent of circulating IL-5 levels, which tend to increase during asthma exacerbations. The drug is also insensitive to the effect of other cytokines such as IL-3 and GM-CSF, due to the profound depletion of eosinophils.<sup>44</sup> All these findings have led to highly promising results in terms of reduction of exacerbations and average dose of OCS, with a response already evident after a single dose. The drug is administered every 4 weeks for the first three doses, then every 8 weeks thereafter.<sup>50</sup>

Data from the ZONDA trial substudy showed a tissue depletion of eosinophils induced by benralizumab greater than other anti-IL-5.<sup>51</sup> In addition, the effect of benralizumab-based ADCC could overcome the problem of the immune complex formation between mepolizumab and IL-5, which may serve as an IL-5 reservoir and thus determine a partial response to treatment (underdosing), as reported by some researchers.<sup>52</sup> The effect of benralizumab on the improvement of FEV<sub>1</sub> is evident, even in patients with fixed airflow obstruction (FAO) and obesity, as highlighted by the *post hoc* analysis of the studies SIROCCO and CALIMA.<sup>53,54</sup> Even if at different levels, a few studies have provided evidence of the benefit of the mAbs on the steroid-sparing effect, as evidenced when comparing the data from the ZONDA<sup>50</sup> and SIRIUS<sup>34</sup> RCTs on benralizumab and mepolizumab, respectively. The former showed that the two benralizumab dosing regimens (30 mg administered subcutaneously either every 4 weeks or every 8 weeks – with the first three doses administered every 4 weeks) significantly reduced the median final oral glucocorticoid doses from baseline by 75%, as compared with a reduction of 25% in the oral glucocorticoid doses in the placebo group ( $p < 0.001$  for both comparisons). On the other hand, the latter showed that the median percentage reduction from baseline in the glucocorticoid dose was 50% in the mepolizumab group (100 mg administered SC every 4 weeks for 20 weeks), as compared with no reduction in the placebo group ( $p = 0.007$ ). Even if direct comparative studies are needed, this may suggest a greater effectiveness of benralizumab as compared to the direct competitor.

Moreover, the pre-filled syringe and the administration every 8 weeks reinforce the drug profile in terms of compliance and usability. In accordance with these findings and on the clinical evidence, the baseline factors that positively impact on response to benralizumab are a higher dose of OCS, frequent asthma exacerbations, nasal polyposis, and forced vital capacity (FVC) <65% predicted.<sup>55</sup> The sustained tissue

depletion of eosinophils induced by benralizumab may raise some concerns regarding the theoretical risk of tumors, infections, and autoimmune diseases. However, several data have confirmed that the absence of eosinophils from mammals is not associated with any pathology.<sup>56</sup> The observation that eosinophil-deficient mice do not show any characteristic syndrome or global health issues strongly supports that under usual laboratory conditions eosinophil does not play a critical role in maintaining mammalian well-being. On the opposite side, the neutrophils deficiency is typically associated with more frequent bacterial infections.<sup>57</sup> The available data suggest that current anti-eosinophil therapies are safe, although long-term studies are needed to confirm their safety.

The possibility of overlapping target population between omalizumab and anti-IL-5, shown in up to 37% of cases,<sup>58</sup> is a critical topic (Figure 2). It is therefore essential to understand the responder profile of each of the two options, and to identify the potential candidates to a treatment switch, although in the absence of head-to-head comparative studies up to now. Meta-analysis data show that the efficacy of omalizumab and mepolizumab is similar in terms of clinical outcomes.<sup>59</sup> Unfortunately, the heterogeneity of selection criteria and the absence of biomarkers specifically predictive of treatment response make the treatment choice a difficult task.

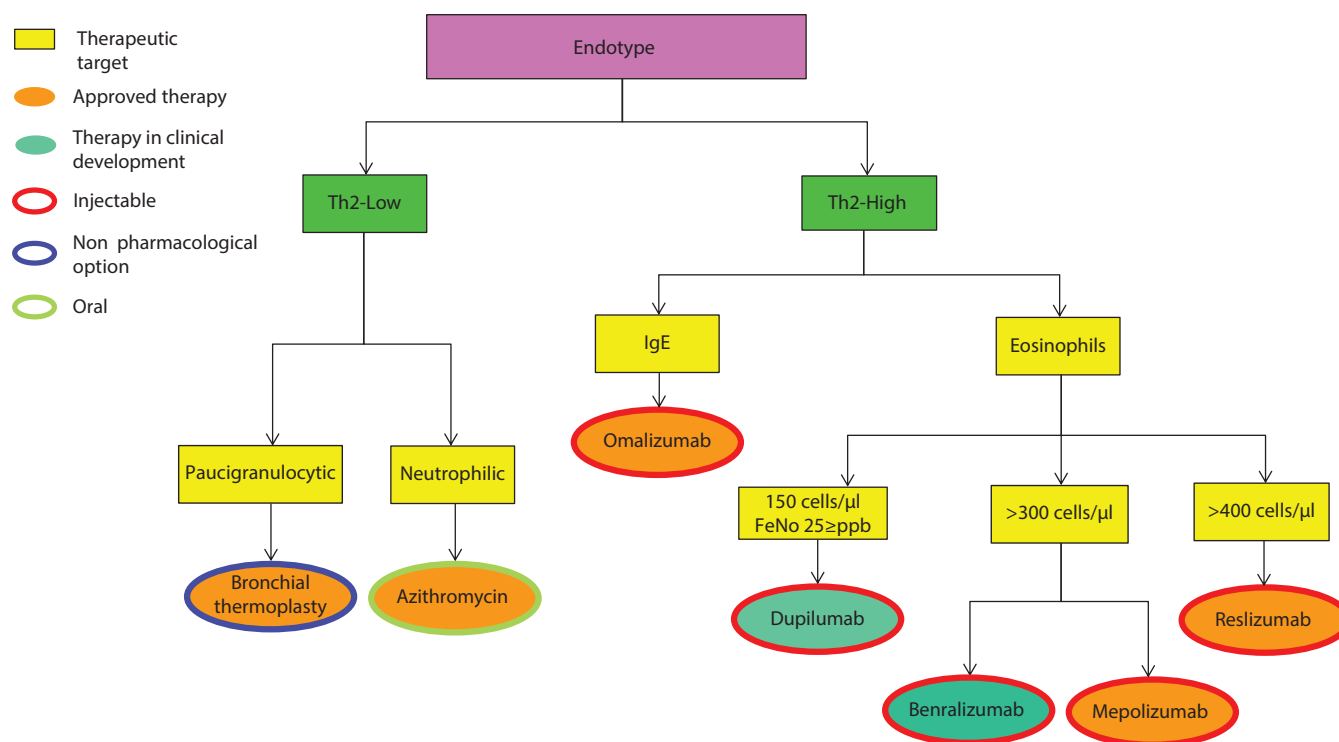
A *post hoc* analysis aiming to evaluate the effect of mepolizumab in patients with severe eosinophilic asthma previously treated with omalizumab showed how high

levels of IgE and the presence of atopy does not reduce the effectiveness of anti-IL-5.<sup>60</sup> Patients with severe eosinophilic asthma responded positively to mepolizumab regardless of the prior use of omalizumab, thus supporting the switch between anti-IgE and anti-IL-5, in case of ineffectiveness of the former, as a potentially effective intervention.

## Blocking IL-4 and IL-13: role of dupilumab

IL-4 and IL-13 are pleiotropic Th2 cytokines, which share a common receptor, IL-4R $\alpha$ , and a common pathway. Dupilumab is a new mAb that inhibits the pro-inflammatory effect of these two cytokines through its interaction with the IL-4  $\alpha$  subunit of the IL-4 receptor.<sup>61</sup> Recent studies investigating dupilumab administered SC at doses ranging from 100 to 300 mg showed a significant decrease in the rate of exacerbations, an improvement of asthmatic symptoms and pulmonary function.<sup>62</sup> A reduction of the inflammatory biomarkers related to the activity of Th2 lymphocytes (TARC levels, eotaxin-3, FeNo) without modifications in the eosinophils count ( $\pm 300$  cells/ $\mu$ L) was also noticed.<sup>63,64</sup> A very recent phase 3 RCT (liberty asthma venture) demonstrated that the greatest efficacy of dupilumab was observed in patients with type 2 profile (blood eosinophil count at baseline  $\geq 150$  per cells/ $\mu$ L and baseline FeNO  $\geq 25$  ppb). Among patients with a blood eosinophil count of  $>300$  cells/ $\mu$ L, treatment with dupilumab

**Figure 2. Severe asthma endotype serving for the correct therapeutic choice.**



IgE, immunoglobulin E; Th2, T helper 2.

resulted in a 65.8% reduction of the severe exacerbation rate compared to the placebo group.<sup>65</sup> In another study (liberty asthma quest), the reduction of glucocorticoids was 70.1% in the dupilumab group, compared to 41.9% in the placebo group. Treatment with this mAb resulted in a 59% reduction in severe exacerbation rate with an increase in FEV<sub>1</sub> of 0.22 L.<sup>66</sup> It is very important to note that in this study patients were recruited regardless to the presence of type 2 biomarkers, such as baseline blood or sputum eosinophil count, FeNO or IgE. These aspects confirm the great potential of dupilumab not only in Th2 high pattern, but also in neglected phenotypes.

However, some concerns about safety have been raised. An increase in the blood eosinophil count up to >3000 cells/μL was reported in 13% of the patients,<sup>64</sup> including anecdotal reports of eosinophilic pneumonia. Type 2 cytokines such as IL-4 and IL-13 have been shown to prime migratory responses of the hematopoietic progenitor cells (HPC). Consequently, the increase of blood eosinophilia could be explained by the blocking of the IL4 and IL13 receptor with loss of lung-homing of eosinophils.<sup>67</sup> Moreover, as Th2 cytokines are powerful suppressors of IL-17 driven-inflammation, Th2-targeted treatment may lead to the amplification of the activity of the opposite Th17 pathway, limiting therapeutic efficacy over time.<sup>68</sup> Large-scale studies are needed to clarify long-term safety issues. Recently, the United States Food and Drug Administration (FDA) approved dupilumab for groups of uncontrolled asthma patients, those with eosinophilic moderate-to-severe asthma phenotype, even those with oral corticosteroid-dependent asthma, regardless of phenotype (<https://www.accessdata.fda.gov/scripts/cder/daf>).

## Ongoing research: failures, promises, and unmet needs

Ligelizumab (QGE031), a new anti-IgE mAb, showed at the first phases of its development higher suppression of free IgE when compared to omalizumab; the same effect was observed also in patients with very high IgE levels.<sup>69</sup> Despite promising initial data, the phase 2 study CQGE031B2201 did not satisfy the primary outcome, as the superiority of QGE031 compared to placebo (Novartis Pharmaceuticals, unpublished data) was not demonstrated.<sup>70</sup> Nevertheless, according to another double-blind RCT parallel groups results, ligelizumab was more effective than omalizumab in terms of skin test positivity suppression and lung function response, demonstrating its potentiality beyond omalizumab.<sup>71</sup> However, the development of ligelizumab has been currently suspended.

Type 2 immunity is regulated by several transcription factors, such as GATA-3, STAT-6, NFAT, IRF4, and c-maf. GATA-3 is one of the six members of the GATA transcription factors family and represents the main regulator in Th2 differentiation.<sup>72</sup> It has been shown to play a key role in mediating the asthmatic immune response, by promoting the production of IL-4, IL-5, and IL-13.<sup>73</sup> Induction of GATA-3 overexpression in T and ILC2

lymphocytes in experimental models leads to an increased allergic airway inflammation.<sup>74</sup> It has also been shown that at least part of the corticosteroid therapeutic activity in the treatment of type 2 inflammation can be attributed to an inhibitory effect on the phosphorylation of GATA-3, which suppresses nuclear translocation of this transcription factor.<sup>75,76</sup>

Recent options targeting GATA-3 belong to the new class of antisense oligonucleotide therapeutics, the 10–23 DNA (deoxyribonucleic acid)zymes (DNAzymes) antisense oligonucleotide, which includes SB010.<sup>77</sup> By cleaving GATA-3 mRNA, SB010 reduces specific cytokine production and thereby exerts its effect on key features of allergic airway inflammation.<sup>74</sup> Based on the overall positive results of the application of GATA-3 DNAzymes in animal models, phase 1 and 2 RCTs were recently performed with inhaled SB010 in patients with uncontrolled allergic asthma and sputum eosinophilia. SB010 demonstrated a significant reduction of Th2-dependent biomarkers such as sputum eosinophilia, serum IL-5, and tryptase levels.<sup>73</sup> Further clinical trials are needed in order to confirm the clinical efficacy of this promising molecule.

Prostaglandin D2 (PGD2) is a prostanoid produced primarily by mastcells in atopic subjects. It exerts a pro-inflammatory effect and induces vasodilatation and increased permeability. Fevipiprant (QAW039) is a PGD2 antagonist of the chemo-attractant receptor-homologous molecule expressed on Th2 cells (CRTH2). The drug, which can bind receptors on the surface of eosinophils, basophils, and T lymphocytes in the blood and tissues, inhibits the migration and activation of these cells in the airway tissues and blocks the PGD2-driven release of the Th2 cytokines.<sup>78</sup> RCTs of phase 2 and 3 have been performed in patients with refractory allergic asthma, and others are in progress. Preliminary data confirm a good safety profile, an improvement in asthma control and FEV<sub>1</sub>, especially in patients with more severe obstruction.<sup>79</sup>

Lebrikizumab (MILR1444A) is a humanized mAb targeting IL-13. In the phase 2 studies, lebrikizumab showed an improvement in pulmonary function and in the control of severe refractory asthma, only in the subgroup of patients with allergic phenotype, including high levels of serum periostin and exhaled FeNO.<sup>80</sup> Subsequently, two parallel phase 3 RCTs were conducted to evaluate the effectiveness and safety of lebrikizumab in patients with uncontrolled asthma (LAVOLTA I and II). LAVOLTA I met its primary endpoint, showing a significant reduction of asthma exacerbations rate in people with higher levels of serum periostin or blood eosinophils. This study also showed a significant improvement in lung function. Unfortunately, LAVOLTA II study did not confirm the same results.<sup>81</sup>

Tralokinumab is another anti-IL-13 mAb, whose development is hampered by the poorly encouraging data emerging from two randomized phase 2b trials. In fact, tralokinumab did not show any significant reduction in exacerbations or improve the Asthma Control Questionnaire (ACQ) score.<sup>82</sup> A *post hoc* analysis showed a greater improvement in FEV<sub>1</sub> in the group



with higher basal IL-13 levels (10 µg/mL), suggesting that the presence of residual IL-13 was associated with a higher response in FEV<sub>1</sub>.<sup>83</sup> Optimistically, it is possible that a more proper patient selection could improve the drug performance; the same issue limited, at the beginning, mepolizumab efficacy when administered to asthmatic patients independently of their phenotype. Three other randomized phase 2 and 3 RCTs (MESOS, STRATOS 1 and 2) have confirmed the ineffectiveness of tralokinumab in asthma, speculating that the role of IL-13 may not be crucial for the control of eosinophilic airway inflammation.<sup>84</sup> In a recent study, adult patients with mild-to-moderate asthma not receiving inhaled corticosteroids (ICS) therapy were randomized to receive lebrikizumab 125 mg SC, placebo SC or montelukast 10 mg orally for 12 weeks.<sup>85</sup> Unfortunately, lebrikizumab did not significantly improve the FEV<sub>1</sub>, probably because the inhibition of IL-13 only did not result in an effective modulation of bronchial inflammation.

Regarding neutrophilic and paucigranulocytic asthma, the treatment options are extremely limited in the field of biologics, as different molecules failed in achieving the primary outcomes. CXCR2-chemokine receptor, a potent chemo-attractant that mediates neutrophil migration in the airways, represents a target currently under investigation. A preliminary study showed a reduction in sputum and blood neutrophils and a better asthma control based on ACQ, but no significant change in FEV<sub>1</sub> was observed in patients with severe asthma treated with SCH527123, a CXCR2 antagonist.<sup>13</sup> Further studies assessed the safety and efficacy of AZD5069, another CXCR2 antagonist, as add-on therapy in patients with severe-uncontrolled asthma.<sup>86</sup> Treatment with this CXCR2-selective antagonist did not reduce the frequency of severe exacerbations, thus raising major doubts about the role of CXCR2-mediated neutrophil recruitment in severe refractory asthma exacerbations and potential clinical benefits.

Recently, stem cell factors and its receptors, including the tyrosine kinase inhibitor (KIT), were recently evaluated because of their critical role to mast cell homeostasis. Mast cells are long-living, tissue-dwelling, hematopoietic effector cells that are implicated in the pathobiologic basis of asthma and are present in patients with severe asthma, in face of glucocorticoid therapy. Their presence correlates with airway hyper-responsiveness and asthma severity.<sup>87</sup> Imatinib, a KIT inhibitor, showed promising results in a RCT, which reported decreasing airway hyperresponsiveness, mast-cell counts, a small but significant increase in FEV<sub>1</sub> and tryptase release, thus suggesting a KIT-dependent process and mast cells contribution to the pathobiological basis of asthma.<sup>88</sup> Currently, further studies on imatinib in asthma are being planned in early clinical trials.

The sialic acid-binding immunoglobulin-like lectins (Siglecs), members of the immunoglobulin gene family, are currently under evaluation for future studies. They selectively regulate early neutrophil recruitment in the lung.<sup>89</sup> Siglec-9 is expressed by human neutrophils and monocytes, as well as

by a minority of natural killer cells. These proteins can interact with antibodies and glycan ligands resulting in neutrophils programmed cell death. In addition, Siglec-E antibody administration abolishes neutrophil recruitment in mouse models of neutrophil lung inflammation. As neutrophils are probably the main cause of the generation and perpetuation of inflammation in the non-Th2 endotype, targeting Siglec-9 could be useful for the treatment of severe asthma and chronic obstructive pulmonary disease (COPD).<sup>90</sup>

## Is precision medicine already outdated?

Severe asthma is characterized by heterogeneity and complexity and is classified according to both phenotypes and endotypes approaches. Nowadays, in contrast with the classical 'one size fits all' approach, precision medicine is based on specific biological profiles guided by biomarkers, which are useful for the development and selection of targeted biological therapies. As the advent of biological therapies with omalizumab, we are witnessing a growing interest in the identification of new biomarkers potentially useful for the selection and treatment guidance of patients. The choice of the right drug for the right patient is becoming increasingly important, considering the partial overlap between the populations eligible for anti-IL-5 mAbs or omalizumab, as mentioned earlier.<sup>60</sup>

Recent advances in the immunological and inflammatory asthma pathways have led to the identification of the alarmins and the key role in the pathogenesis of asthma. The airway epithelium has been shown to play a central role in the modulation of complex inflammatory processes.<sup>91,92</sup> The cytokines produced by the epithelium can be released following the exposure to pro-inflammatory external stimuli. Among these cytokines, the triad IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) promotes immune responses and are involved in delaying the asthmatic reactions after exposure to allergens. TSLP is an epithelial-cell-derived cytokine produced after environmental and proinflammatory stimuli.<sup>93,94</sup> The PATHWAY study further investigated the clinical and biological role of TSLP in patients with moderate-to-severe uncontrolled asthma.<sup>95</sup> This was a randomized, placebo-controlled, dose-ranging trial for tezepelumab, a fully human first-in-class anti-TSLP mAb, where patients with various levels of blood eosinophilia were also included. The use of tezepelumab at various doses (70 mg every 4 weeks, 210 mg every 4 weeks or 280 mg every 2 weeks) showed a reduction of the exacerbation rate in the treatment groups of 61%, 71%, and 66%, respectively, as compared to the placebo group ( $p < 0.001$  for all comparisons). The same results were observed regardless blood eosinophil count, Th2 status, or FeNO levels at enrollment.

The FDA granted tezepelumab as a 'breakthrough' biological drug for the treatment of severe asthma, thus speeding up

its registration process. A Breakthrough Therapy definition is designed to fasten the development and regulatory review of drugs that have proven to be effective in respect of a clinically significant endpoint compared to available drugs ([www.fda.gov/news-events/press-features/20180518-fda-awards-astrazeneca-and-amgens-tezepelumab-breakthrough-designation](http://www.fda.gov/news-events/press-features/20180518-fda-awards-astrazeneca-and-amgens-tezepelumab-breakthrough-designation)).

The favorable response to this promising drug, almost completely independent of the patient phenotyping, could provocatively overcome the classic ‘tailored therapy’ or ‘precision medicine’ paradigm. However, further and much larger studies are needed to confirm these findings.

## Developments in related diseases

In COPD, as well as in asthma, there are several inflammatory phenotypes. So far, acceptable results have only been obtained in the eosinophilic ones. In subjects with moderate-to-severe COPD and blood eosinophil counts of 300 cells/ $\mu$ L or greater, a major risk of exacerbations and steroids responsiveness is reported.<sup>96</sup> Two phase 3 RCTs on mepolizumab as add-on therapy in patients with eosinophilic COPD (METREX and METREO)<sup>96</sup> showed interesting findings. Patients with a blood eosinophil count of 150 cells/ $\mu$ L or more at screening, or 300 cells/ $\mu$ L or higher during the previous 12 months were included. The results demonstrated a significant reduction (23%) of exacerbations in 25% of patients with a baseline blood eosinophil count at 300 cells/ $\mu$ L. The clinical efficacy was observed only in the 70% of the severe exacerbations treated with OCS.

A RCT with benralizumab, including patients with COPD and blood eosinophil higher than 300 cells/ $\mu$ L, is ongoing.<sup>97</sup> A phase 3 study investigating lebrikizumab is also recruiting patients; however, given the disappointing results on severe asthma, there will probably be no favorable outcome in COPD either.<sup>81</sup>

Chronic rhinosinusitis, both CRS with nasal polyposis (CRSwNP) and without nasal polyposis (CRSsNP) is an inflammatory disease of the nose and paranasal sinuses, characterized by elevated levels of IL-5, IL-13, and eosinophils. In a randomized, double-blind, placebo-controlled study, omalizumab demonstrated positive results in patients with CRSwNP, even in non-allergic patients.<sup>98</sup> A recent study in a real-life setting confirmed the efficacy of omalizumab in severe allergic asthma with co-existent CRSwNP.<sup>99</sup> This is probably due to the presence of a local mucosal production of IgE. Regarding the anti-IL-5 mAbs, mepolizumab, and reslizumab, excellent results have been demonstrated especially in patients with eosinophilic nasal polyps, whereas nasal IL-5 levels did not predict a good response.<sup>40,100</sup> Another biologic drug, benralizumab, may have the advantage of not targeting only eosinophilia but basophils, present at high levels in patients with CRSwNP.<sup>101</sup> It will be necessary to verify through large-scale studies the real efficacy of benralizumab and its theoretical superiority over competitors.

A phase 2 study (ClinicalTrials.gov identifier: NCT01920893) demonstrated the efficacy of dupilumab in reducing nasal polyps when added to mometasone furoate nasal spray.<sup>102</sup> Significant improvements were also observed for the SinoNasal Outcome test for sense and smell. Two RCTs are currently underway to evaluate the efficacy of this mAb in reducing the severity of nasal congestion/obstruction and endoscopic nasal polyp score (NPS) (ClinicalTrials.gov identifier: NCT02912468 and NCT02898454).

## Economic burden of asthma and biological therapies

Asthma is a growing public health problem and the costs of management and treatment are increasing. Clinical trials have demonstrated that the control of severe asthma, which can be achieved through innovative therapies, can reduce the overall economic burden, even if the single cost of the drug increases.<sup>103</sup> It is also shown that the cost of asthma significantly increases with the reduction of disease control. However, it is possible to obtain important savings on direct costs through the correct management of patients and the appropriate use of new therapeutic options.<sup>104</sup>

Because of the economic impact and significant increase of direct costs, the availability of new treatment options for severe asthma, such as omalizumab, bronchial thermoplasty (BT), and mepolizumab, has required great attention in the selection and management of potentially eligible patients. Moreover, in some countries, drug-economic analyses (CEAs) are necessary as a requirement to obtain the reimbursement of biological drugs, due to their high cost.

The most considered outcomes of the published studies included exacerbations, mortality, health-related quality of life (HRQoL), use of healthcare resources, and direct costs. Most of the studies on omalizumab conclude that anti-IgE mAb achieves clinical outcomes especially when administered in patients with difficult-to-treat asthma. This drug is cost effective according to the majority of studies, especially if targeted to very severe subgroups and with price discounts.<sup>105</sup> Direct costs could be partly offset by the reduction of the expenses incurred by the health service (e.g. hospitalizations), a reduction of indirect costs and improvement of quality of life.<sup>106,107</sup>

Regarding mepolizumab, there are few pharmacoeconomic data because of its recent introduction in clinical practice. An interesting CEA conducted by the ICER Group was based on a simulation model of asthma outcomes and costs in a representative population of patients eligible to mepolizumab therapy.<sup>108</sup> The incremental cost effectiveness of mepolizumab was evaluated by gathering drug cost estimates derived from current prices and estimates of reductions in asthma exacerbations and OCS use from relevant clinical trial data. According to the authors of this analysis, based on current acquisition prices, the cost-effectiveness estimates are unfavorable, as they exceed the commonly cited thresholds.

Further doubts arise from the lack of clinical trials evaluating the long-term benefits. To obtain a value correlated to the clinical benefit, a discount of two-thirds to three-quarters from the current price list of mepolizumab would be necessary.

A recent study investigated the potential cost effectiveness of mepolizumab.<sup>109</sup> A Markov model was used to determine the incremental cost per quality of life-year (QALY) obtained for mepolizumab plus standard of care (SoC) and for SoC alone. The population, including adults with severe eosinophilic asthma, was defined on a lifetime horizon. Based on the results of this study, to achieve a cost-effectiveness of about \$150,000 for QALY, mepolizumab would require a discount of over 60% on the price.

So far, only one study aimed at investigating whether reslizumab can be cost effective. The authors used a Markov model to compare the cost effectiveness of add-on reslizumab with the standard of care from the US societal perspective over a 5-year time horizon. The conclusion was that the improvement in QoL and exacerbation rate with reslizumab is associated with high costs, making reslizumab unlikely to be cost-effective at the \$200,000 willingness-to-pay (WTP) threshold.<sup>110</sup>

Another study defined and compared the cost-effectiveness of the newest medical treatment strategies for severe refractory asthma, such as omalizumab, mepolizumab, and BT.<sup>111</sup> The authors used a model including a hypothetical cohort of 10,000 patients with a 10-year horizon. In patients who are responders to biological treatment, the addition of bronchial thermoplasty was not cost-effective. Mepolizumab without BT was the most cost-effective option for biological responders. However, BT proved to be a cost-effective treatment option in the group of nonresponders to biologicals.

## Conclusions

Nowadays, much more than in the past, pharmacological research has promised safe and effective therapeutic options

for patients with severe, uncontrolled asthma, a very complex and heterogeneous entity. It should not be neglected that the management of severe asthma still represents a challenge, because the asthma mortality rate is still unacceptable,<sup>112</sup> and because poor adherence to therapy was demonstrated not only in patients with mild symptoms, but also in those with higher levels of severity.<sup>113</sup> Furthermore, acute and chronic side effects still have a major impact in those patients taking OCS treatment. Moreover, the associated costs, especially in patients that are unfit for treatment with biological drugs, are high.<sup>114,115</sup> Some new and effective therapeutic options, such as dupilumab, will soon be available, and this will probably increase the direct costs associated with pharmacological treatment. Understanding the disease mechanisms and using predictive biomarkers will allow customization of the approach to disease management and will guide the clinician in the choice of right drug, among the increasingly numerous therapeutic options. It will reduce the number of uncontrolled patients and avoid therapeutic failures. The presence of overlapping target populations for omalizumab and anti-IL-5 requires an increasing effort in understanding the differences among the underlying pathways of these molecules. It is increasingly clear that omalizumab remains the gold standard for refractory allergic asthma, especially for the 'early onset' phenotype, while anti-IL-5 mAbs are indicated in eosinophilic asthma with comorbidities such as nasal polyposis. Among the latter, benralizumab seems to have a small advantage linked to its peculiar mechanism of action, to its rapid onset of effect, and to the greater steroid-sparing effect, as discussed earlier. Beyond indirect evaluations, comparative head-to-head studies will be essential to allow a correct treatment choice and to avoid empirical or marketing-oriented selection strategies. However, non-Th2 endotype asthma remains a major challenge, as research has not provided so far many treatment options. In the future, the phenotype will obtain the focus it deserves.

**Contributions:** All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

**Disclosure and potential conflicts of interest:** Francesco Menzella participated in contracted research and clinical trials for Novartis and Sanofi, he has received lecture fees and advisory board fees from AstraZeneca, BoehringerIngelheim, Chiesi, GlaxoSmithKline, Mundipharma and Novartis. The other authors report no conflicts of interest in this work. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors are available for download at <http://www.drugsincontext.com/wp-content/uploads/2018/11/dic.212561-COI.pdf>

**Acknowledgments:** None.

**Funding declaration:** There was no funding associated with the preparation of this article.

**Copyright:** Copyright © 2018 Menzella F, Bertolini F, Biava M, Galeone C, Scelfo C, Caminati M. Published by Drugs in Context under Creative Commons License Deed CC BY NC ND 4.0 which allows anyone to copy, distribute, and transmit the article provided it is properly attributed in the manner specified below. No commercial use without permission.

**Correct attribution:** Copyright © 2018 Menzella F, Bertolini F, Biava M, Galeone C, Scelfo C, Caminati M. <https://doi.org/10.7573/dic.212561>. Published by Drugs in Context under Creative Commons License Deed CC BY NC ND 4.0.

**Article URL:** <https://www.drugsincontext.com/severe-refractory-asthma-current-treatment-options-and-ongoing-research>

**Correspondence:** Francesco Menzella, Department of Medical Specialties, Pneumology Unit, Azienda USL di Reggio Emilia, IRCCS, Viale Amendola 2, 42122 Reggio Emilia, Italy. [francesco.menzella@ausl.re.it](mailto:francesco.menzella@ausl.re.it)

**Provenance:** invited; externally peer reviewed.

**Submitted:** 26 September 2018; **Peer review comments to author:** 12 November 2018; **Revised manuscript received:** 14 November 2018; **Accepted:** 16 November 2018; **Publication date:** 5 December 2018.

**Drugs in Context** is published by BioExcel Publishing Ltd. Registered office: Plaza Building, Lee High Road, London, England, SE13 5PT.

BioExcel Publishing Limited is registered in England Number 10038393. VAT GB 252 7720 07.

For all manuscript and submissions enquiries, contact the Editor-in-Chief [gordon.mallarkey@bioexcelpublishing.com](mailto:gordon.mallarkey@bioexcelpublishing.com)

For all permissions, rights and reprints, contact David Hughes [david.hughes@bioexcelpublishing.com](mailto:david.hughes@bioexcelpublishing.com)

## References

1. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*. 2014;43:343–373. Erratum in: *Eur Respir J*. 2018;52(1). <http://dx.doi.org/10.1183/09031936.00202013>
2. Pakhale S, Mulpuru S, Boyd M. Optimal management of severe/refractory asthma. *Clin Med Insights Circ Respir Pulm Med*. 2011;5:37–47. <http://dx.doi.org/10.4137/CCRP.M.55535>
3. Papi A, Brightling C, Pedersen SE, Reddel HK. Asthma. *Lancet*. 2018;391(10122):783–800. [http://dx.doi.org/10.1016/S0140-6736\(17\)33311-1](http://dx.doi.org/10.1016/S0140-6736(17)33311-1)
4. Ivanova JI, Bergman R, Birnbaum HG, Colice GL, Silverman RA, McLaurin K. Effect of asthma exacerbations on health care costs among asthmatic patients with moderate and severe persistent asthma. *J Allergy Clin Immunol*. 2012;129: 1229–1235. <http://dx.doi.org/10.1016/j.jaci.2012.01.039>
5. Heaney LG, Brightling CE, Menzies-Gow A, Stevenson M, Niven RM. Refractory asthma in the UK: cross-sectional findings from a UK multicentre registry. *Thorax*. 2010;65:787–794. <http://dx.doi.org/10.1136/thx.2010.137414>
6. Volmer T, Effenberger T, Trautner C, Buhl R. Consequences of long-term oral corticosteroid therapy and its side-effects in severe asthma in adults: a focused review of the impact data in the literature. *Eur Respir J*. 2018;52(4): pii: 1800703. <http://dx.doi.org/10.1183/13993003.00703-2018>
7. de Benedictis FM, Bush A. Corticosteroids in respiratory diseases in children. *Am J Respir Crit Care Med*. 2012;185(1):12–23. <http://dx.doi.org/10.1164/rccm.201107-1174CI>
8. Gibson PG, Simpson JL, Saltos N. Heterogeneity of airway inflammation in persistent asthma: evidence of neutrophilic inflammation and increased sputum interleukin-8. *Chest*. 2001;119:1329–1336. PubMed PMID: 11348936
9. Lötvalld J, Akdis CA, Bacharier LB, et al. Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. *J Allergy Clin Immunol*. 2011;127(2):355. <http://dx.doi.org/10.1016/j.jaci.2010.11.037>
10. Licari A, Castagnoli R, Brambilla I, et al. Asthma endotyping and biomarkers in childhood asthma. *Pediatr Allergy Immunol Pulmonol*. 2018;31(2):44–55. <http://dx.doi.org/10.1089/ped.2018.0886>
11. Caminati M, Pham DL, Bagnasco D, Canonica GW. Type 2 immunity in asthma. *World Allergy Organ J*. 2018;11(1):13. <http://dx.doi.org/10.1089/ped.2018.0886>
12. Desai M, Oppenheimer J. Elucidating asthma phenotypes and endotypes: progress towards personalized medicine. *Ann Allergy Asthma Immunol*. 2016;116(5):394–401. <http://dx.doi.org/10.1016/j.anai.2015.12.024>
13. Wechsler ME. Current and emerging biologic therapies for asthma and COPD. *Respir Care*. 2018;63(6):699–707. <http://dx.doi.org/10.4187/respcare.06322>
14. Nair P, Gaga M, Zervas E, et al. Safety and efficacy of a CXCR2 antagonist in patients with severe asthma and sputum neutrophils: a randomized, placebo-controlled clinical trial. *Clin Exp Allergy*. 2012;42(7):1097–1103. <http://dx.doi.org/10.1111/j.1365-2222.2012.04014.x>
15. Choy DF, Hart KM, Borthwick LA, et al. TH2 and TH17 inflammatory pathways are reciprocally regulated in asthma. *Sci Transl Med*. 2015;7(301):301ra129. <http://dx.doi.org/10.1126/scitranslmed.aab3142>
16. Aron JL, Akbari O. Regulatory T cells and type 2 innate lymphoid cell-dependent asthma. *Allergy*. 2017;72(8):1148–1155. <http://dx.doi.org/10.1111/all.13139>
17. Samitas K, Delimpoura V, Zervas E, et al. Anti-IgE treatment, airway inflammation and remodelling in severe allergic asthma: current knowledge and future perspectives. *Eur Respir Rev*. 2015;24(138):594–601. <http://dx.doi.org/10.1183/16000617.00001715>
18. Humbert M, Busse W, Hanania NA, et al. Omalizumab in asthma: an update on recent developments. *J Allergy Clin Immunol Pract*. 2014;2(5):525–536. <http://dx.doi.org/10.1016/j.jaip.2014.03.010>
19. Rodrigo GJ, Neffen H, Castro-Rodriguez JA. Efficacy and safety of subcutaneous omalizumab vs placebo as add-on therapy to corticosteroids for children and adults with asthma: a systematic review. *Chest*. 2011;139(1):28–35. <http://dx.doi.org/10.1378/chest.10-1194>
20. Menzella F, Piro R, Facciolo N, et al. Long-term benefits of omalizumab in a patient with severe non-allergic asthma. *Allergy Asthma Clin Immunol*. 2011;7(1):9. <http://dx.doi.org/10.1186/1710-1492-7-9>



21. Forester JP, Calabria CW. Local production of IgE in the respiratory mucosa and the concept of entropy: does allergy exist in nonallergic rhinitis? *Ann Allergy Asthma Immunol.* 2010;105(4):249–255. <http://dx.doi.org/10.1016/j.anai.2010.02.001>
22. Busse WW, Morgan WJ, Gergen PJ, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *N Engl J Med.* 2011;364(1):1005–1015. <http://dx.doi.org/10.1056/NEJMoa1009705>
23. Teach SJ, Gill MA, Togias A, et al. Preseasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations. *J Allergy Clin Immunol.* 2015;136(6):1476–1485. <http://dx.doi.org/10.1016/j.jaci.2015.09.008>
24. Ledford D, Busse W, Trzaskoma B, et al. A randomized multicenter study evaluating Xolair persistence of response after long-term therapy. *J Allergy Clin Immunol.* 2017;140(1):162–169.e2. <http://dx.doi.org/10.1016/j.jaci.2016.08.054>
25. Hanania NA, Wenzel S, Rosén K, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. *Am J Respir Crit Care Med.* 2013;187(8):804–811. <http://dx.doi.org/10.1164/rccm.201208-1414OC>
26. Casale TB, Chipps BE, Rosen K, et al. Response to omalizumab using patient enrichment criteria from trials of novel biologics in asthma. *Allergy.* 2018;73:490–497. <http://dx.doi.org/10.1111/all.13302>
27. Humbert M1, Taillé C, Mala L, et al. Omalizumab effectiveness in patients with severe allergic asthma according to blood eosinophil count: the STELLAIR study. *Eur Respir J.* 2018;51(5): pii: 1702523. <http://dx.doi.org/10.1183/13993003.02523-2017>
28. Menzella F, Galeone C, Formisano D, et al. Real-life efficacy of omalizumab after 9 years of follow-up. *Allergy Asthma Immunol Res.* 2017;9(4): 368–372. <http://dx.doi.org/10.4168/aair.2017.9.4.368>
29. Menzella F, Facciolo N, Piro R, et al. Clinical and pharmacoeconomic aspects of omalizumab: a 4-year follow-up. *Ther Adv Respir Dis.* 2012;6(2):87–95. <http://dx.doi.org/10.1177/1753465811429478>
30. Legrand F, Klion AD. Biologic therapies targeting eosinophils: current status and future prospects. *J Allergy Clin Immunol Pract.* 2015;3(2):167–174. <http://dx.doi.org/10.1016/j.jaip.2015.01.013>
31. Leckie MJ, ten Brinke A, Khan J, et al. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. *Lancet.* 2000;356(9248):2144–2148. [http://dx.doi.org/10.1016/S0140-6736\(00\)03496-6](http://dx.doi.org/10.1016/S0140-6736(00)03496-6)
32. Flood-Page P, Menzies-Gow A, Phipps S, et al. Anti-IL-5 treatment reduces deposition of ECM proteins in the bronchial subepithelial basement membrane of mild atopic asthmatics. *J Clin Invest.* 2003;112(7):1029–1036. <http://dx.doi.org/10.1172/JCI17974>
33. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med.* 2014;371(13): 1198–1207. <http://dx.doi.org/10.1056/NEJMoa1403290>
34. Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet.* 2012;380(9842):651–659. [http://dx.doi.org/10.1016/S0140-6736\(12\)60988-X](http://dx.doi.org/10.1016/S0140-6736(12)60988-X)
35. Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med.* 2014;371(13):1189–1197. <http://dx.doi.org/10.1056/NEJMoa1403291>
36. Chupp GL, Bradford ES, Albers FC, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. *Lancet Respir Med.* 2017;5(5):390–400. [http://dx.doi.org/10.1016/S2213-2600\(17\)30125-X](http://dx.doi.org/10.1016/S2213-2600(17)30125-X)
37. Ortega HG, Yancey SW, Mayer B, et al. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. *Lancet Respir Med.* 2016;4(7):549–556. [http://dx.doi.org/10.1016/S2213-2600\(16\)30031-5](http://dx.doi.org/10.1016/S2213-2600(16)30031-5)
38. Lugogo N, Domingo C, Chanez P, et al. Long-term efficacy and safety of mepolizumab in patients with severe eosinophilic asthma: a multi-center, open-label, phase IIIb study. *Clin Ther.* 2016;38(9):2058–2070.e1. <http://dx.doi.org/10.1016/j.clinthera.2016.07.010>
39. Castro M, Mathur S, Hargreave F, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. *Am J Respir Crit Care Med.* 2011;184(10):1125–1132. <http://dx.doi.org/10.1164/rccm.201103-0396OC>
40. Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med.* 2015;3(5):355–366. [http://dx.doi.org/10.1016/S2213-2600\(15\)00042-9](http://dx.doi.org/10.1016/S2213-2600(15)00042-9)
41. Weinstein SF, Germinaro M, Bardin P, et al. Efficacy of reslizumab with asthma, chronic sinusitis with nasal polyps and elevated blood eosinophils. *J Allergy Clin Immunol.* 2016;137(2):AB86. <http://dx.doi.org/10.1016/j.jaci.2015.12.409>
42. Murphy K, Jacobs J, Bjermer L, et al. Long-term safety and efficacy of reslizumab in patients with eosinophilic asthma. *J Allergy Clin Immunol Pract.* 2017;5(6):1572–1581.e3. <http://dx.doi.org/10.1016/j.jaip.2017.08.024>
43. Mukherjee M, Aleman Paramo F, Kjarsgaard M, et al. Weight-adjusted Intravenous reslizumab in severe asthma with inadequate response to fixed-dose subcutaneous mepolizumab. *Am J Respir Crit Care Med.* 2018;197(1):38–46. <http://dx.doi.org/10.1164/rccm.201707-1323OC>
44. Kolbeck R, Kozhich A, Koike M, et al. MEDI-563, a humanized anti-IL-5 receptor alpha mAb with enhanced antibody-dependent cell-mediated cytotoxicity function. *J Allergy Clin Immunol.* 2010;125(6):1344–1353. <http://dx.doi.org/10.1016/j.jaci.2010.04.004>



45. Menzella F, Lusuardi M, Galeone C, Facciolo N, Zucchi L. The clinical profile of benralizumab in the management of severe eosinophilic asthma. *Ther Adv Respir Dis*. 2016;10(6):534–548. <http://dx.doi.org/10.1177/1753465816667659>
46. Laviolette M, Gossage DL, Gauvreau G, et al. Effects of benralizumab on airway eosinophils in asthmatic patients with sputum eosinophilia. *J Allergy Clin Immunol*. 2013;132(5):1086–1096. <http://dx.doi.org/10.1016/j.jaci.2013.05.020>
47. Ghazi A, Trikha A, Calhoun WJ. Benralizumab – a humanized mAb to IL-5R alpha with enhanced antibody-dependent cell-mediated cytotoxicity – a novel approach for the treatment of asthma. *Expert Opin Biol Ther*. 2012;12(1):113–118. <http://dx.doi.org/10.1517/14712598.2012.642359>
48. Castro M, Wenzel SE, Bleecker ER, et al. Benralizumab, an anti-interleukin 5 receptor alpha monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. *Lancet Respir Med*. 2014;2(11):879–890. [http://dx.doi.org/10.1016/S2213-2600\(14\)70201-2](http://dx.doi.org/10.1016/S2213-2600(14)70201-2)
49. FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor  $\alpha$  monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2016;388(10056):2128–2141. [http://dx.doi.org/10.1016/S0140-6736\(16\)31322-8](http://dx.doi.org/10.1016/S0140-6736(16)31322-8)
50. Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting  $\beta_2$ -agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet*. 2016;388(10056):2115–2127. [http://dx.doi.org/10.1016/S0140-6736\(16\)31324-1](http://dx.doi.org/10.1016/S0140-6736(16)31324-1)
51. Nair P, Wenzel S, Rabe KF, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. *N Engl J Med*. 2017;376(25):2448–2458. <http://dx.doi.org/10.1056/NEJMoa1703501>
52. Lugogo N, Kline JN, Hirsch I, et al. Benralizumab improves morning peak expiratory flow while reducing oral corticosteroid dosages for patients with severe, uncontrolled asthma in the ZONDA phase III trial. *Am J Respir Crit Care Med*. 2018;197:A2488.
53. Mukherjee M, Nair P. Autoimmune responses in severe asthma. *Allergy Asthma Immunol Res*. 2018;10(5):428–447. <http://dx.doi.org/10.4168/aa.2018.10.5.428>
54. Chipps BE, Hirsch I, Trudo F, et al. Demographics, clinical characteristics, and response to benralizumab treatment for patients with severe, eosinophilic asthma and fixed airflow obstruction. *Am J Respir Crit Care Med*. 2018;197:A2489
55. Trudo F, Hirsch I, Gopalan G, et al. Impact of body mass index on efficacy of benralizumab in patients with severe, uncontrolled eosinophilic asthma: pooled analysis of the SIROCCO and CALIMA trials. *Am J Respir Crit Care Med*. 2018;197:A2490.
56. Bleecker ER, Wechsler ME, FitzGerald JM, et al. Baseline patient factor impact on the clinical efficacy of benralizumab for severe asthma. *Eur Respir J*. 2018 Aug 23. pii: 1800936. <http://dx.doi.org/10.1183/13993003.00936-2018>
57. Gleich GJ, Klion AD, Lee JJ, et al. The consequences of not having eosinophils. *Allergy*. 2013;68(7):829–835. <http://dx.doi.org/10.1111/all.12169>
58. Bogomolski-Yahalom V, Matzner Y. Disorders of neutrophil function. *Blood Rev*. 1995;9:183–190. [http://dx.doi.org/10.1016/0268-960X\(95\)90024-1](http://dx.doi.org/10.1016/0268-960X(95)90024-1)
59. Albers FC, Müllerová H, Gunsoy NB, et al. Biologic treatment eligibility for real-world patients with severe asthma: The IDEAL study. *J Asthma*. 2018;55(2):152–160. <http://dx.doi.org/10.1080/02770903.2017.1322611>
60. Nachev Z, Krishnan A, Mashtare T, et al. Omalizumab versus mepolizumab as add-on therapy in asthma patients not well controlled on at least an inhaled corticosteroid: a network meta-analysis. *J Asthma*. 2018;55(1):89–100. <http://dx.doi.org/10.1080/02770903.2017.1306548>
61. Magnan A, Bourdin A, Prazma CM, et al. Treatment response with mepolizumab in severe eosinophilic asthma patients with previous omalizumab treatment. *Allergy*. 2016;71(9):1335–1344. <http://dx.doi.org/10.1111/all.12914>
62. Gandhi NA, Pirozzi G, Graham NMH. Commonality of the IL-4/IL-13 pathway in atopic diseases. *Expert Rev Clin Immunol*. 2017;13(5):425–437. <http://dx.doi.org/10.1080/1744666X.2017.1298443>
63. Vatrella A, Fabozzi I, Calabrese C, et al. Dupilumab: a novel treatment for asthma. *J Asthma Allergy*. 2014;7:123–130. <http://dx.doi.org/10.2147/JAA.S52387>
64. Wenzel S, Ford L, Pearlman D, et al. Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med*. 2013;368(26):2455–2466. <http://dx.doi.org/10.1056/NEJMoa1304048>
65. Wenzel S, Castro M, Corren J, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting  $\beta_2$  agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose ranging trial. *Lancet*. 2016;388(10039):31–44. [http://dx.doi.org/10.1016/S0140-6736\(16\)30307-5](http://dx.doi.org/10.1016/S0140-6736(16)30307-5)
66. Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med*. 2018;378(26):2486–2496. <http://dx.doi.org/10.1056/NEJMoa1804092>
67. Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med*. 2018;378(26):2475–2485. <http://dx.doi.org/10.1056/NEJMoa1804093>
68. Salter BM, Sehmi R. Hematopoietic processes in eosinophilic asthma. *Chest*. 2017;152(2):410–416. <http://dx.doi.org/10.1016/j.chest.2017.01.021>

69. Newcomb DC, Peebles RS Jr. Th17-mediated inflammation in asthma. *Curr Opin Immunol*. 2013;25(6):755–760. <http://dx.doi.org/10.1016/j.coi.2013.08.002>
70. Arm JP, Bottoli I, Skerjanec A, et al. Pharmacokinetics, pharmacodynamics and safety of QGE031 (ligelizumab), a novel high-affinity anti-IgE antibody, in atopic subjects. *Clin Exp Allergy*. 2014;44(11): 1371–1385. <http://dx.doi.org/10.1111/cea.12400>
71. Novartis Pharmaceuticals. Efficacy and safety of QGE031 versus Placebo and Omalizumab in Patients Aged 18–75 Years With Asthma; 2012. <https://clinicaltrials.gov/ct2/show?term=CQGE031B2201>. Accessed August 18, 2018. NLM Identifier: NCT01716754.
72. Gauvreau GM, Arm JP, Boulet LP, et al. Efficacy and safety of multiple doses of QGE031 (ligelizumab) versus omalizumab and placebo in inhibiting allergen-induced early asthmatic responses. *J Allergy Clin Immunol*. 2016;138(4):1051–1059. <http://dx.doi.org/10.1016/j.jaci.2016.02.027>
73. Maneechotesuwan K, Xin Y, Ito K, et al. Regulation of Th2 cytokine genes by p38 MAPK-mediated phosphorylation of GATA-3. *J Immunol*. 2007;178:2491–2498. <http://dx.doi.org/10.4049/jimmunol.178.4.2491>
74. Zhu J, Paul WE. Peripheral CD4+ T-cell differentiation regulated by networks of cytokines and transcription factors. *Immunol Rev*. 2010;238(1):247–262. Erratum in: *Immunol Rev*. 2011;240(1):317.
75. KleinJan A, Klein Wolterink RG, Levani Y, et al. Enforced expression of Gata3 in T cells and group 2 innate lymphoid cells increases susceptibility to allergic airway inflammation in mice. *J Immunol*. 2014;192:1385–1394. <http://dx.doi.org/10.4049/jimmunol.1301888>
76. Maneechotesuwan K, Yao X, Ito K, et al. Suppression of GATA-3 nuclear import and phosphorylation: a novel mechanism of corticosteroid action in allergic disease. *PLoS Med*. 2009;6:e1000076. <http://dx.doi.org/10.1371/journal.pmed.1000076>
77. Liberman AC, Druker J, Refojo D, et al. Glucocorticoids inhibit GATA-3 phosphorylation and activity in T cells. *FASEB J*. 2009;23:1558–1571. <http://dx.doi.org/10.1096/fj.08-121236>
78. Garn H, Renz H. GATA-3-specific DNase – a novel approach for stratified asthma therapy. *Eur J Immunol*. 2017;47(1):22–30. <http://dx.doi.org/10.1002/eji.201646450>
79. Chevalier E, Stock J, Fisher T, et al. Cutting edge: chemoattractant receptor-homologous molecule expressed on Th2 cells plays a restricting role on IL-5 production and eosinophil recruitment. *J Immunol*. 2005;175(4):2056–2060. <http://dx.doi.org/10.4049/jimmunol.175.4.2056>
80. White C, Wright A, Brightling C. Fevipiprant in the treatment of asthma. *Expert Opin Investig Drugs*. 2018 Feb;27(2):199–207. <http://dx.doi.org/10.1080/13543784.2018.1432592>
81. Maselli DJ, Keyt H, Rogers L. Profile of lebrikizumab and its potential in the treatment of asthma. *J Asthma Allergy*. 2015;8:87–92. <http://dx.doi.org/10.2147/JAA.S69932>
82. Hanania NA, Korenblat P, Chapman KR, et al. Efficacy and safety of lebrikizumab in patients with uncontrolled asthma (LAVOLTA I and LAVOLTA II): replicate, phase 3, randomised, double-blind, placebo controlled trials. *Lancet Respir Med*. 2016;4(10):781–796. [http://dx.doi.org/10.1016/S2213-2600\(16\)30265-X](http://dx.doi.org/10.1016/S2213-2600(16)30265-X)
83. Piper E, Brightling C, Niven R, et al. A phase II placebo-controlled study of tralokinumab in moderate-to-severe asthma. *Eur Respir J*. 2013;41(2):330–338. <http://dx.doi.org/10.1183/09031936.00223411>
84. Brightling CE, Chanez P, Leigh R, et al. Efficacy and safety of tralokinumab in patients with severe uncontrolled asthma: a randomised, double-blind, placebo-controlled, phase 2b trial. *Lancet Respir Med*. 2015;3(9):692–701. [http://dx.doi.org/10.1016/S2213-2600\(15\)00197-6](http://dx.doi.org/10.1016/S2213-2600(15)00197-6)
85. Chung KF. Tralokinumab unsuccessful for management of severe, uncontrolled asthma. *Lancet Respir Med*. 2018;6(7):480–481. [http://dx.doi.org/10.1016/S2213-2600\(18\)30194-2](http://dx.doi.org/10.1016/S2213-2600(18)30194-2)
86. Korenblat P, Kerwin E, Leshchenko I, et al. Efficacy and safety of lebrikizumab in adult patients with mild-to-moderate asthma not receiving inhaled corticosteroids. *Respir Med*. 2018;134:143–149. <http://dx.doi.org/10.1016/j.rmed.2017.12.006>
87. O’Byrne PM, Metev H, Puu M, et al. Efficacy and safety of a CXCR2 antagonist, AZD5069, in patients with uncontrolled persistent asthma: a randomised, double-blind, placebo-controlled trial. *Lancet Respir Med*. 2016;4(10):797–806. [http://dx.doi.org/10.1016/S2213-2600\(16\)30227-2](http://dx.doi.org/10.1016/S2213-2600(16)30227-2)
88. Brightling CE, Bradding P, Symon FA, et al. Mast-cell infiltration of airway smooth muscle in asthma. *N Engl J Med*. 2002;346:1699–1705. <http://dx.doi.org/10.1056/NEJMoa012705>
89. Cahill KN, Katz HR, Cui J, et al. KIT inhibition by imatinib in patients with severe refractory asthma. *N Engl J Med*. 2017;376(20):1911–1920. <http://dx.doi.org/10.1056/NEJMoa1613125>
90. McMillan SJ, Sharma RS, McKenzie EJ, et al. Siglec-E is a negative regulator of acute pulmonary neutrophil inflammation and suppresses CD11b  $\beta$ 2-integrin-dependent signaling. *Blood*. 2013;121(11):2084–2094. <http://dx.doi.org/10.1182/blood-2012-08-449983>
91. Chen Z, Bai FF, Han L, et al. Targeting neutrophils in severe asthma via Siglec-9. *Int Arch Allergy Immunol*. 2018;175(1–2):5–15. <http://dx.doi.org/10.1159/000484873>
92. Vareille M, Kieninger E, Edwards MR, et al. The airway epithelium: soldier in the fight against respiratory viruses. *Clin Microbiol Rev*. 2011;24:210–229. <http://dx.doi.org/10.1128/CMR.00012-11>

93. Holgate ST. Epithelium dysfunction in asthma. *J Allergy Clin Immunol*. 2007;120:1233–1244. <http://dx.doi.org/10.1016/j.jaci.2007.10.025>
94. Al-Sajee D, Oliveria JP, Sehmi R, et al. Antialarmins for treatment of asthma: future perspectives. *Curr Opin Pulm Med*. 2018;24(1):32–41. <http://dx.doi.org/10.1097/MCP.0000000000000443>
95. Ziegler SF, Artis D. Sensing the outside world: TSLP regulates barrier immunity. *Nat Immunol*. 2010;11:289–293. <http://dx.doi.org/10.1038/ni.1852>
96. Corren J, Parnes JR, Wang L, et al. Tezepelumab in adults with uncontrolled asthma. *N Engl J Med*. 2017;377(10):936–946. <http://dx.doi.org/10.1056/NEJMoa1704064>
97. Yun JH, Lamb A, Chase R, et al. Blood eosinophil count thresholds and exacerbations in patients with chronic obstructive pulmonary disease. *J Allergy Clin Immunol*. 2018;141(6):2037–2047. <http://dx.doi.org/10.1016/j.jaci.2018.04.010>
98. Pavord ID, Chanez P, Criner GJ, et al. Mepolizumab for eosinophilic chronic obstructive pulmonary disease. *N Engl J Med*. 2017;377:1613–1629. <http://dx.doi.org/10.1056/NEJMoa1708208>
99. Gevaert P, Calus L, Van Zele T, et al. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. *J Allergy Clin Immunol*. 2013;131(1):110–116. <http://dx.doi.org/10.1016/j.jaci.2012.07.047>
100. Bidder T, Sahota J, Rennie C, Lund VJ, Robinson DS, Kariyawasam HH. Omalizumab treats chronic rhinosinusitis with nasal polyps and asthma together—a real life study. *Rhinology*. 2018;56(1):42–45. <http://dx.doi.org/10.4193/Rhin17.139>
101. Gevaert P, Van Bruaene N, Cattaert T, et al. Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. *J Allergy Clin Immunol*. 2011; 128(5):989–995. <http://dx.doi.org/10.1016/j.jaci.2011.07.056>
102. Mahdavinia M, Carter RG, Ocampo CJ, et al. Basophils are elevated in nasal polyps of patients with chronic rhinosinusitis without aspirin sensitivity. *J Allergy Clin Immunol*. 2014;133(6):1759–1763. <http://dx.doi.org/10.1016/j.jaci.2013.12.1092>
103. Bachert C, Mannent L, Naclerio RM, et al. Effect of subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis: a randomized clinical trial. *JAMA*. 2016;315:469–479. <http://dx.doi.org/10.1001/jama.2015.19330>
104. Antonicelli L, Bucca C, Neri M, et al. Asthma severity and medical resource utilisation. *Eur Respir J*. 2004;23(5):723–729. <http://dx.doi.org/10.1183/09031936.04.00004904>
105. Accordini S, Corsico AG, Braggion M, et al. The cost of persistent asthma in Europe: an international population-based study in adults. *Int Arch Allergy Immunol*. 2013;160(1):93–101. <http://dx.doi.org/10.1159/000338998>
106. Queen RB, Sheehan DN, Whittington MD, et al. Cost-Effectiveness of biological asthma treatments: a systematic review and recommendations for future economic evaluations. *Pharmacoeconomics*. 2018 May 8. <http://dx.doi.org/10.1007/s40273-018-0658-x>
107. Menzella F, Facciolo N, Piro R, et al. Clinical and pharmacoeconomic aspects of omalizumab: a 4-year follow-up. *Ther Adv Respir Dis*. 2012;6(2):87–95. <http://dx.doi.org/10.1177/1753465811429478>
108. Menzella F, Zucchi L, Piro R, et al. A budget impact analysis of bronchial thermoplasty for severe asthma in clinical practice. *Adv Ther*. 2014;31(7):751–761. <http://dx.doi.org/10.1007/s12325-014-0135-7>
109. Institute for Clinical and Economic Review (2015) ICER Draft Reports on Nucala® (Mepolizumab) for Asthma and Tresiba® (Insulin Degludec) for Diabetes Posted for Public Comment Edit. <https://icer-review.org/announcements/icer-draft-reports-on-nucala-mepolizumab-for-asthma-and-tresiba-insulin-degludec-for-diabetes-posted-for-public-comment-edit/>. Accessed September 15, 2018.
110. Whittington MD, McQueen RB, Ollendorf DA, et al. Assessing the value of mepolizumab for severe eosinophilic asthma: a cost-effectiveness analysis. *Ann Allergy Asthma Immunol*. 2017;118(2):220–225. <http://dx.doi.org/10.1016/j.anai.2016.10.028>
111. Lam J, Hay J, Salcedo J, et al. A cost-effectiveness analysis of reslizumab in the treatment of poorly controlled eosinophilic asthma. *J Asthma*. 2018;1–10. <http://dx.doi.org/10.1080/02770903.2018.1500584>
112. Bogart M, Roberts A, Wheeler S. Cost effectiveness of refractory asthma treatment strategies: a decision tree analysis. In: ISPOR 20th Annual International Meeting, Philadelphia, PA, USA, 2015.
113. Bourdin A, Molinari N, Vachier I, et al. Mortality: a neglected outcome in OCS-treated severe asthma. *Eur Respir J*. 2017;50(5):pii: 1701486. <http://dx.doi.org/10.1183/13993003.01486-2017>
114. Lee J, Tay TR, Radhakrishna N, et al. Nonadherence in the era of severe asthma biologics and thermoplasty. *Eur Respir J*. 2018;51(4):pii: 1701836. <http://dx.doi.org/10.1183/13993003.01836-2017>
115. Lefebvre P, Duh MS, Lafeuille MH, et al. Acute and chronic systemic corticosteroid-related complications in patients with severe asthma. *J Allergy Clin Immunol*. 2015;136(6):1488–1495. <http://dx.doi.org/10.1016/j.jaci.2015.07.046>